Medical and Pediatric Oncology 26:318–324 (1996)

Survival of Childhood Leukemia in Singapore

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The objective of this study was to evaluate the treatment outcome of children with acute leukemias at a university hospital in Singapore. Between January 1988 and January 1994, 66 children were treated, comprising 13 cases of acute myeloid leukemia (AML) and 53 of acute lymphoblastic leukemia (ALL). The 2-year disease-free survival (DFS) was computed according to the Kaplan-Meier method. The results showed that the survival for AML was poor, with a 2-year DFS of only 30%. The major cause of death for AML was leukemia and leukemia-related complications, such as hemorrhage and severe infections. In contrast, a 62% 2-year DFS was achieved for ALL. It was found that marked hepatosplenomegaly (enlarged liver and/or spleen ≥10 cm below the costal margin) at presentation correlated with a significantly shortened survival in our patients with ALL. The major cause for treatment failure in ALL was recurrence of disease. We conclude that the DFS for our patients with ALL at 2 years was fair. The treatment results for AML were poor, but the numbers are too small to make any definite conclusions.

Key words: acute leukemia, acute myeloid leukemia, AML, acute lymphoblastic leukemia, ALL, disease free survival, DFS

INTRODUCTION

Since the introduction of effective treatment for childhood acute lymphoblastic leukemia (ALL) in the late 1960s, the long-term survival rate has increased from 50% to 70% [1–3]. The results for acute myeloid leukemia (AML), although less spectacular, have more recently shown a similar improvement. For example, the 5-year survival rate of the UK Medical Research Council AML trials improved from 12% for children treated from 1972 to 1982 to 45% for those treated between 1985 and 1990 [4]. Whilst there have been mamy reports of treatment outcome of childhood acute leukemias from countries in Europe and North America, there are few reports from the Asian continent [5]. In this article we report our experience with childhood acute leukemias at the Department of Paediatrics, National University of Singapore, between January 1988 and January 1994.

MATERIALS AND METHODS

Patients

All 66 consecutive patients with acute leukemia under the age of 12 years presenting to our unit between January 1988 and January 1994 were entered into this study. Thirteen had AML (19.7%) and 53 had ALL (80.3%). Clinical data on the patients are given in Tables I and II. Complete remission was defined as 5% or less leukemic blasts, by morphological examination, in the bone marrow at the end of induction.

Morphological Examinations

The diagnosis of AML and ALL was made according to the criteria proposed by the French-American-British Cooperative Working Group [6–8]. May-Grünwald-Giemsa stain and histochemical studies, including periodic acid Schiff's stain (PAS), myeloperoxidase (MPO), Sudan black B (SBB), alpha-naphthol butyrate esterase (NSE), and acid phosphatase (aPh), were used for examinations of the leukemic blasts.

Immunophenotyping

Alkaline phosphatase anti-alkaline phosphatase (APAAP) staining was used for immunophenotyping of the leukemic blasts in those entered before May 1991 according to a method described previously [9]. Two-color flow cytometry (FACScan; Becton-Dickinson, San Jose, CA) was employed after May 1991. Monoclonal antibodies used for immunophenotyping were purchased from Dakopatts (Dakopatts, Glostrup, Denmark) for APAAP and from Becton-Dickinson for flow cytometry. Immunophenotyping was performed on 41 ALL patients

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Received November 9, 1994; accepted July 27, 1995.

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TABLE I. Clinical Characteristics of Patients With AML

Patient	Age (months)	Sex	Hematological parameters (peripheral blood) Hb	WBC	Plt	Blast %	FAB subtype	Outcome[a]
1	45	M	10.6	93.6	46	89	M1	2, D
2	27	M	4.5	894.0	29	95	M4	0.5, D
3	12	M	9.4	29.0	49	25	M4	7, D
4	18	M	5.3	2.3	15	38	M4	23, D
5	57	F	6.3	20.0	40	24	M4	18, D
6	4	M	12.4	16.0	53	91	M6	0.5, D
7	106	M	8.3	58.6	37	41	M2	2, D
8	24	M	16.9	7.8	54	37	M5	15, D
9	14	F	10.4	32.4	48	36	M7	7, D
10	52	F	10.4	32.4	58	43	M3	30, S
11	15	F	6.8	1.8	74	16	M5	18, S
12	110	F	8.5	35.6	57	34	M3	2, D
13	12	M	9.5	25.3	68	42	M7	27, S

Median age = 24 months; mean age = 38.2 months.
Median follow-up = 18 months; longest follow-up = 30 months.
[a]Number indicates time (months) from diagnosis.
D = death; S = disease-free survival.

with the following panel of monoclonal antibodies: HLA DR, CD34, CD33, CD13, CD14, CD15, CD7, CD2, CD4, CD8, CD10, CD19, CD20, CD41, and CD61. The patients with ALL were subdivided into three phenotypic subgroups: CD10+ ALL included those with expression of CD10 in more than 20% of leukemic blasts, CD10− ALL included those with expression of less than 20% of leukemic blasts in the diagnostic bone marrow [10], and T-cell leukemia (TCL) included those with predominant expression of one or more T-cell–related surface markers, such as CD2, CD5, CD7, CD3, CD4, and CD8, and positive reaction of the leukemic blasts to acid phosphatase.

Treatment Protocols

Acute lymphoblastic leukemia. Induction therapy consisted of daily dexamethasone and weekly vincristine for the first 4–5 weeks, L-asparaginase (ASP) at 3 doses/week for the first 3 weeks, weekly vincristine (VCR), weekly daunorubicin 2–3 doses, and weekly triple intrathecal therapy [methotrexate (MTX), hydrocortisone, and cytarabine] for 4–6 weeks. Two different types of sanctuary therapy were given. Children younger than 24 months and older children who are not at high rish for central nervous system (CNS) relapse received six courses of intermediate-dose MTX (1 g/m^2) plus triple intrahecal (IT) injections, that is, MTX, hydrocortisone, and cytarabine (ara-C), and ASP. Children older than 24 months at high risk for CNS relapse were given cranial irradiation 18,000 cGy and triple IT injections. Intensification was given to all patients (4 doses for low-risk and 12 doses for high-risk patients). This consisted of alternative weeks of VCR/cyclophosphamide and teniposide/ara-C. Maintenance therapy consisted of daily 6-mercaptopurine (6-MP) and weekly MTX, with 3-monthly pulses of VCR, dexamethasone, and triple IT injections. The whole course of treatment last for 2 years, and is summarized in Table III.

Acute myeloid leukemia. Induction consisted of daunorubicin 45 mg/m^2 for 3 days and cytarabine 100 mg/m^2/day by continuous intravenous infusion for 7 days. Consolidation consisted of the above-mentioned regimen plus etoposide and high-dose ara-C of 3 g/m^2. The treatment scheme for AML is given in Table IV. We have recently started to use the POG 8101 protocol in two patients [11].

Statistical Analysis

As the number of patients entered was small and the follow-up for the late entries was short, 2-year disease-free survival (DFS) was chosen as the indicator of treatment outcome. The survival and selected prognostic factors in ALL were plotted by the Kaplan-Meier method. Differences in survival between prognostic groups were tested by the Wilcoxon rank sum tests, and the 95% confidence interval was used. For patients with ALL, prognostic factors were chosen according to well-recognized factors, including white blood cell count (WBC) at entry, age, and gender. The patients were stratified according to WBC, WBC <10,000, WBC >10,000 <20,000, and WBC >20,000; age at presentation, <24 months and ≥24 but <120 months old; and expression of CD10, CD10+ ALL and CD10− ALL. In addition, another factor analyzed was marked hepatosplenomegaly, as defined by enlargement of the liver and/or spleen measuring ≥10 cm below the costal margin at presentation. Interactions between different prognostic factors on the influence of DFS were tested by the Cox proportional

TABLE II. Clinical Characteristics of Patients With ALL

Patients	Age (month)/ Sex	Hematol. parameters (peripheral blood) Hb	WBC	Plt	Blast %	Phenotypic subgroups CD10+	CD10−[a]	TCL	Marked organomegaly[b]	Relapse[c]	Outcome[d]
1	123/M	7.8	39.0	80	17	N	Y	N	N	N	80, CR
2	38/M	5.8	69.0	10	92	N	Y	N	N	N	80, CR
3	32/F	8.8	2.2	45	8	Y	N	N	Y	BM	80, CR
4	40/M	5.1	52.8	12	32	N	Y	N	Y	BM, T	12, D
5	38/F	5.3	7.2	213	20	Y	N	N	N	N	76, CR
6	47/M	6.9	3.8	24	22	Y	N	N	Y	N	76, CR
7	34/F	7.0	21.2	11	8	Y	N	N	N	N	70, CR
8	31/M	4.6	9.0	90	46	Y	N	N	N	N	70, CR
9	47/F	7.8	79.2	63	62	Y	N	N	Y	BM	22, D
10	48/F	7.5	21.0	58	74	Y	N	N	N	BM	21, D
11	48/M	8.6	25.5	40	73	Nt	Nt	Nt	N	BM	13, L
12	51/F	7.6	4.3	38	42	Y	N	N	Y	N	68, CR
13	36/F	12.9	4.6	19	10	Y	N	N	N	N	68, CR
14	60/M	11.9	15.4	32	13	Y	N	N	N	N	68, CR
15	36/M	8.9	21.7	46	57	Y	N	N	N	N	55, CR
16	67/F	8.5	24.4	35	66	Y	N	N	N	N	60, CR
17	65/M	6.8	14.9	55	58	Y	N	N	N	N	60, CR
18	50/M	7.6	13.3	12	15	N	N	Y	N	N	59, CR
19	36/M	8.5	23.2	21	65	Y	N	N	N	BM	8, D
20	106/F	7.9	140.0	35	95	N	Y	N	N	BM	31, D
21	35/M	10.2	11.9	27	50	N	Y	N	Y	N	1, D
22	68/M	9.2	8.1	92	26	Y	N	N	Y	BM	7, D
23	35/F	4.6	59.2	17	45	Y	N	N	N	BM	9, D
24	45/M	5.6	5.9	36	26	N	N	Y	Y	BM	18, D
25	68/M	8.3	5.0	71	38	Y	'N	N	Y	BM	18, L
26	139/F	8.9	50.8	28	58	N	N	Y	Y	N	0.5, D
27	47/F	8.8	47.9	62	85	Y	N	N	N	N	38, CR
28	56/F	7.4	10.7	60	44	Y	N	N	N	N	37, CR
29	44/F	8.1	12.1	52	63	Y	N	N	N	N	36, CR
30	119/F	9.3	8.0	24	48	N	Y	N	N	BM	15, D
31	83/M	7.6	17.2	48	61	Y	N	N	N	N	35, CR
32	71/M	3.3	262.9	22	92	N	Y	N	Y	N	23, CR
33	65/F	4.4	48.2	41	93	Y	N	N	N	N	21, CR
34	68/F	8.7	115.1	42	49	Y	N	N	N	N	20, CR
35	124/M	7.3	126.5	69	89	N	Y	N	Y	N	20, CR
36	100/F	8.2	65.5	83	76	Y	N	N	N	N	19, CR
37	20/F	5.5	8.1	58	5	Y	N	N	N	N	19, CR
38	59/M	6.3	75.6	86	92	Y	N	N	N	N	18, CR
39	60/M	5.0	14.0	94	58	Y	N	N	N	N	18, CR
40	109/M	6.5	3.2	84	23	Y	N	N	N	N	14, CR
41	14/M	10.1	13.8	123	39	Y	N	N	N	N	8, CR
42	96/M	8.3	15.9	74	28	Y	N	N	N	N	8, CR
43	30/M	7.4	12.3	66	47	Y	N	N	N	N	78, CR
44	79/F	9.3	16.2	58	37	Y	N	N	N	N	73, CR
45	28/M	6.5	10.3	83	30	Y	N	N	N	N	60, CR
46	57/F	8.6	13.2	79	41	Y	N	N	N	N	55, CR
47	43/M	8.2	9.4	73	26	Y	N	N	N	N	41, CR
48	19/F	11.1	14.8	87	42	Y	N	N	N	N	36, CR
49	39/F	9.5	12.9	62	35	Y	N	N	N	N	29, CR
50	18/F	7.9	16.3	70	27	Y	N	N	N	N	24, CR
51	21/F	8.0	21.2	61	19	Y	N	N	N	N	29, CR
52	8/F	7.7	9.4	88	50	Y	N	N	N	N	18, CR
53	20/M	10.3	11.6	67	29	Y	N	N	N	N	16, CR

Median age = 47 months; mean age = 59.1 months; median follow-up = 28 months.
[a]CD10(−) ALL indicates reactivity to CD10 mAb (cALLA) was <20% of leukemic blasts, but positive for CD19 without evidence for T-cell leukemia or AML.
[b]Marked organomegaly includes those with enlarged liver and/or spleen ≥10 cm below the costal margin.
[c]No relapse if not otherwise indicated.
[d]Numbers indicate period (months) from diagnosis to the date of analysis.
NT = not tested; BM = bone marrow relapse; T = testicular; CR = continuous complete remission; D = death; L = lost to follow-up.

TABLE III. Treatment Regimen for ALL

	Drug	Dose[a]	Route	Schedule
Induction	Dexamethasone	6 mg	PO	Daily × 28
	Vincristine	1.5 mg[b]	IV bolus	Weekly × 4
	Asparaginase	10,000 U	IV infusion or IM	Days 29, 32, 36, 39, 43
Consolidation	Vincristine	1.5 mg[b]	IV bolus	Days 1, 15, (29, 43, 57, 71)
	Cyclophosphamide	300 mg	IV bolus	Days 1, 15, (29, 43, 57, 71)
	Teniposide	150 mg	IV infusion over 2 h	Days 8, 22 (36, 50, 64, 78)
	Cytosar	300 mg	IV bolus	Days 8, 22 (36, 50, 64, 78)
Sanctuary	Vincristine	1.5 mg	IV bolus	Days 1, 15, 29, 43, 57, 71
	Methotrexate	1000 mg 1/3 slow bolus, 2/3 infusion over 24 h	IV	Days 2, 16, 30, 44, 58, 72
	Asparaginase	10,000 U	IV or IM	Days 4, 18, 32, 46, 60, 74
	Leucovorin	12 mg	IV	Every 6 h × 4, beginning 24 h after end of methotrexate
	Methotrexate			Days 1, 15, 29, 43, 57, 71
	Age <1	6 mg	IT	
	Age 1–2	8 mg		
	Age 2–3	10 mg		
	Age >3	12 mg		
	Hydrocortisone			Days 1, 15, 29, 43, 57, 71
	Age <1	6 mg	IT	
	Age 1–2	8 mg		
	Age 2–3	10 mg		
	Age >3	12 mg		
	Cytosar		IT	Days 1, 15, 29, 43, 57, 71
	Age <1	12 mg		
	Age 1–2	16 mg		
	Age 2–3	20 mg		
	Age >3	24 mg		
Maintenance	Mercaptopurine	50 mg	PO	Daily
	Methotrexate	20 mg	PO	Weekly
	Vincristine	1.5 mg[b]	IV bolus	Every 3 months, 2 weekly doses
	Triple IT	As above	IT	Every 3 months
	Dexamethasone	6 mg	PO	Every 3 months, wtih vincristine, for 2 weeks each time

[a]All doses are per m^2 except IT drugs.
[b]2.0 mg maximun.

TABLE IV. Treatment Regimen for AML

	Drug	Dose[a]	Route	Schedule
Induction (2 courses)	Daunorubicin	45 mg	IV	Days 1, 2, 3
	Cytosar	100 mg	IV continuous infusion over 24 h days 1–7	
Consolidation course 1	Etoposide	250 mg	IV infusion	Days 1, 2, 3
	Cytosar	100 mg	IV infusion over 24 h	Days 1–7
Consolidation course 2	Cytosar	3000 mg	IV infusion	12 hourly × 6 doses

[a]All doses are per m^2.

hazards model in all combinations. For example, interactions between marked hepatosplenomegaly and WBC, age, gender, and reactivity to CD10 were studied in order to reveal any possible correlations between the factors. The computer program package used was SAS 6.0 (Cary, NC) [12].

RESULTS

Disease-Free Survival in AML

AML was diagnosed 19.7% of the cases in this study. The complete remission rate for AML was 46%. The 2-year DFS was 30% (±12.8%) (Fig. 1). The two early

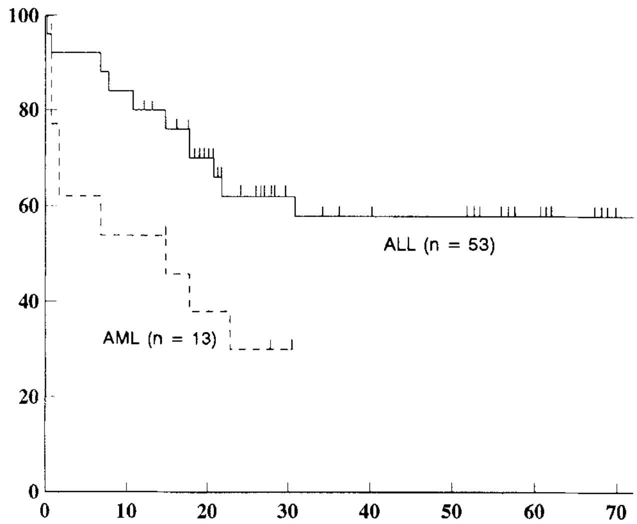

Fig. 1. Disease-free survival for patients with ALL and AML. Solid line, ALL; broken line, AML.

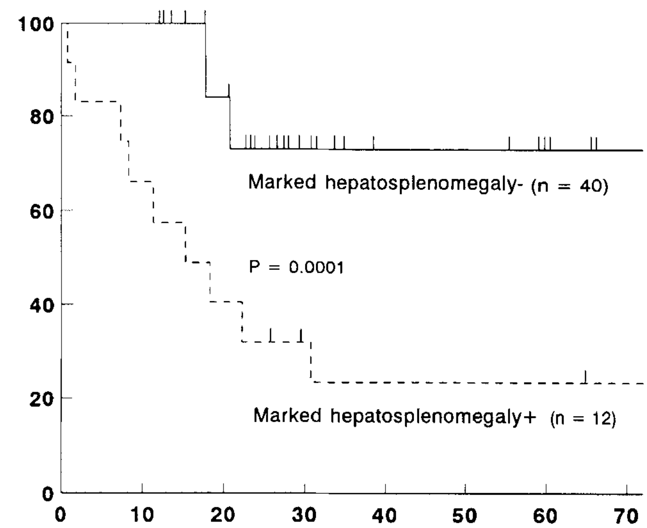

Fig. 2. Disease-free survival for patients without/with marked hepatosplenomegaly at presentation (the definition of "marked hepatosplenomegaly" is given in Materials and Methods). The solid line represents patients without marked hepatosplenomegaly at presentation, and the broken line represents patients with marked hepatosplenomegaly at presentation.

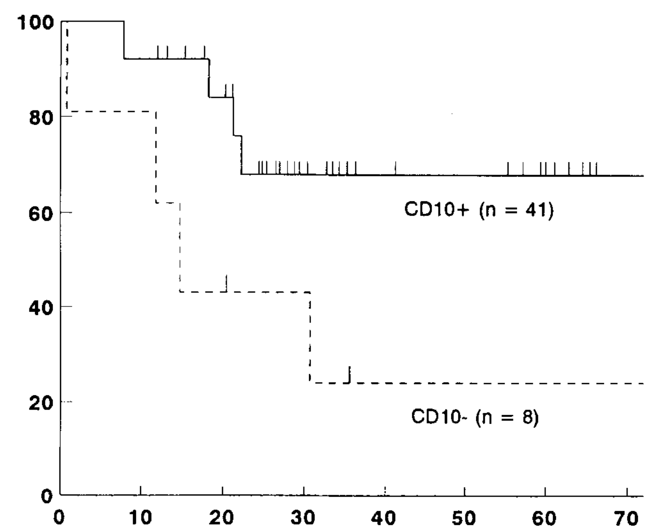

Fig. 3. Disease-free survival for CD10+ and CD10− B precursor ALL. Solid line; CD10+ ALL; broken line; CD10− ALL.

deaths (cases 2 and 6) were due to cerebral and pulmonary hemorrhage, respectively. Cases 1 and 7 died from severe infections secondary to chemotherapy-related leukopenia. Partial remission was achieved in cases 3 and 9, in which full-blown leukemia recurred within 3 months from diagnosis and both subsequently died from leukemia. In the three disease-free survivors, cases 10 and 11 had intensified chemotherapy with autologous bone marrow rescue incorported with a melphalan conditioning regimen according to the protocol described by Tiedemann et al., [13]. Case 13, a 12-month-old boy with Down's syndrome, was treated using the POG 8101 protocol without bone marrow transplantation.

Outcome in ALL

There were 53 patients with ALL (80.1%). The clinical features of the patients with ALL are summarized in Table II. The complete remission rate after induction therapy was 96.2%. The 2-year DFS was 62% (±6.6%) (Fig. 1). The two early deaths (cases 21 and 26) were caused by acute renal failure resulting from the tumor lysis syndrome.

Prognostic Factors

Hepatosplenomegaly. Marked hepatosplenomegaly ⩾10 cm subcostally at diagnosis was documented in 12 of 53 ALL cases (22.6%). This was the most significant prognostic predictor in our patients with ALL, with a 2-year DFS of 72% (±7.0%) in those without marked hepatosplenomegaly vs. 33% (±13.6%) in those with *hepatosplenomegaly* (P = 0.0001, Fig. 2).In addition marked hepatosplenomegaly was found to be independent of other prognostic factors studied, which included WBC, age, gender, and immunophenotype.

Surface antigen expression and prognosis in ALL. The immunophenotype of the leukemic blasts was assessed at diagnosis in 52 of 53 patients with ALL. Three had T-cell leukemia (TCL) and 49 had B precursor ALL, including 41 CD10+ ALL and 8 CD10− ALL. The 2-year DFS of CD10+ ALL was better than CD10− ALL: 68% (±7.2%) vs. 44% (±16.5%) (P = 0.08) (Fig. 3). Only one patient with TCL remained free of disease at 59 months, but this number was too small for further analysis.

Other prognostic factors. Age, gender, and total white cell count at diagnosis were all analyzed. However, none of these factors showed any significance in 2-year DFS (results not shown).

Leukemia Relapse

Leukemia relapse occurred in 12 of 42 (28.6%) ALL cases in our study. Among these, 11 had isolated bone marrow relapse, whilst one had concomitant bone marrow and testicular relapse (case 4). Three relatively early relapses occurred (cases 19, 22, and 23) during early maintenance (within 1 month of commencement of maintenance), and all three patients died of leukemia. Seven patients relapsed at later stages while receiving continuation treatment, and two relapsed after cessation of treatment (cases 10 and 20). All patients who relapsed were given reinduction therapy. However, only one (case 3) responded well to reinduction therapy and remained free of disease at 80 months from diagnosis (70 months from relapse). Nine eventually died from leukemia within 6 months of relapse. Bone marrow transplantation was not done in any of these cases, either because of inability to achieve a second complete remission, or lack of HLA-compatible sibling donors.

DISCUSSION

Patients with AML comprised 19.7% of all cases of acute leukemia in the current study. This was similar to the figures from other groups with much larger patient numbers [14–16]. In our experience, there was no improvement in AML survival between 1973 and 1983 [17]. Complete remission was achieved in 46% patients with AML. The early deaths seen in AML were all caused by hemorrhage and infections. These observations indicate that further improvement in both treatment intensification and supportive care are needed to achieve a better survival.

With advances in modern chemotherapy, greater than 60% prolonged DFS (>5 years) can be achieved in childhood ALL [2,3]. In our study, the 2-year DFS was 62%, although significantly shorter in those presenting with marked hepatosplenomegaly, including the two early deaths (ALL cases 21 and 26). Marked hepatosplenomegaly appeared to be independent of the other factors analyzed, such as age, gender, WBC, and immunophenotype. This was similar to the previous observations by Hammond et al. [18]. The prognostic importance of tumor load, as reflected by a markedly enlarged liver and/or spleen, may justify more intensive therapy in this group of patients. In studies involving larger number of patients, CD10 positivity has been constantly found to correlate with a longer DFS than CD10− B precursor ALL [19–22]. The 2-year DFS was also found to be more favorable in CD10+ ALL compared with CD10− ALL in our patients, although not statistically significant.

There were 12 patients who relapsed. A second remission was achieved in all 12 patients. However, only one patient was free of disease at 80 months. The rest suffered from further relapses and died from leukemia. It was interesting to note that all the deaths in this current study occurred before 32 months from initial diagnosis.

We conclude from our study that the treatment outcome for AML with our current therapeutic protocol was unsatisfactory. The 2-year DFS for ALL was comparable or better than other pediatric oncology centers in Asia [5]. In this study tumor burden as reflected by pronounced hepatosplenomegaly was shown to be an independent predictor for the prognosis in ALL, and more intensification in treatment may need to be given for this group of patients in future. The expression of CD10 in the leukemic blasts, although to a lesser degree, also tended to be a more favorable factor for DFS in ALL. Leukemia relapse was the major cause of treatment failure, and further intensification of the initial therapy may lead to a lower relapse rate. More effective relapse therapy is also needed.

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